UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/664,958	09/18/2000	Iya Trakht	60240/JPW/SHS	4881

7590 09/26/2002

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/26/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/664,958	Applicant(s) TRAKHT ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-18 are pending and under examination.

Specification

2. The disclosure is objected to because of the following informalities:

a. The specification contains numerous places which recite "ATCC Accession No. _____". The correct ATCC number should be added.

b. The specification on page 103-129 contains claims. The specification should not reference the claim numbers because they can be changed during prosecution.

c. The specification should add the corresponding SEQ ID Nos: to the sequences in the specification, for example page 20, lines 27 and 31 and in the Brief description of the Drawings.

d. Applicant is requested to review all pages of the specification for the above listed objections as they appear to be numerous.

e. The NIH grant no is missing from page 1, line 2.

f. The ATCC address on page 39, lines 17-19 should be updated to be "10801 University Boulevard, Manassas, VA 20110-2209".

g. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an antibody having the exact chemical identity of 27.B1 and 27.F7 are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H

sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species 27B1 and 27.F7. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant's referral to the ATCC numbers in the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809

regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing

the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

5. Claims 6 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the

breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an antibody which binds to the same epitope as 27.B1 and 27.F7. The specification teaches the antibodies 27.B1 and 27.F7 and the antibodies bind to a protein called TIP-2. The specification fails to enable the epitope to which the antibodies bind.

As taught in Greenspan et al (Nature Biotechnology 7:936-937 (1999)) defining epitopes is not as easy as it seems (page 937). Epitopes have been defined in terms of the spatial organization of residues that make contact with a ligand and the structural characterization of the molecular interface for the binding of the molecules to define the epitope boundaries (page 937 middle of page). The epitope defined in this manner will likely include residues that contact the ligand but are energetically neutral or even destabilizing to binding. "In addition, a priori it will not include any residue that makes no contact with a ligand but whose substitution may profoundly effect ligand recognition through influence on the stability of the free form of the macromolecule, or participation in long-range allosteric effects". "Even when the residues making contacts with ligands are known with certainty, say from the crystal structure of the complex, the question remains with regard to the energetic involvement of each residue (page 936 right column, first paragraph). Therefore, "amino acids should be recognized to have multiple ways of contributing to a noncovalent interaction" (page 937, middle of page). As evidenced by Greenspan et al a number of factors not primarily related to the

contours of the contacts of the molecules contribute to the free energy change, sometimes profoundly.

Westhof et al (Nature 311:123-126, 1984) also teach the difficulty of defining epitopes, especially conformationally dependent epitopes. Westhof et al teach that clearly discontinuous epitopes cannot be studied with antibodies specific to short linear peptides and cannot be identified in linear plots of flexibility along the protein chain (see page 125).

Therefore, due the unpredictability of defining the epitopes to which antibodies bind as evidenced from Greenspan et al and Westhof et al and in view of the lack of guidance and examples in the specification, one skilled in the art would not know how to practice the broadly claimed invention without undue experimentation.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 2, 8, 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Vries et al (PNAS 95:12340-12345, 1998) and Rousset et al (Oncogene 16:643-654, 1998) and as evidenced by the specification, and further in view of Campbell (Monoclonal antibody technology, Elsevier Science Publishers, pages 1-32, 1986) and Harlow et al (antibodies, A laboratory manual, Cold Spring Harbor Laboratory, page 322, 1988).

The claims recite a monoclonal antibody that binds to TIP-2 and the antigen recognized by antibody 27.B1 and 27.F7, wherein the antibody is a murine antibody, wherein the antibody is labeled with a radioactive isotope for imaging and therapy.

De Vries et al and Rousset et al both teach the TIP-2 protein as evidenced from the specification at page 173-174. The protein of TIP-2 is also called GIPC which is taught by De Vries (see figure 1) and Rousset et al. De Vries et al and Rousset et la do

not teach a monoclonal antibody to TIP-2 or a labeled antibody. These deficiencies are made up for by the teachings of Campbell and Harlow et al.

Campbell et al teach production of murine monoclonal antibodies.

Harlow et al teach labeling methods for detection.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a monoclonal antibody to the protein of De Vries et al and Rousset et al by the method of Campbell and to label the antibody as taught by Harlow et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a monoclonal antibody to the protein of De Vries et al and Rousset et al by the method of Campbell and to label the antibody as taught by Harlow et al because Campbell et al teach "It is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" (see page 29). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a monoclonal antibody to the protein of De Vries et al and Rousset et al by the method of Campbell and to label the antibody as taught by Harlow et al because Harlow teach routine methods for labeling antibodies for detection and the label can be iodine, enzymes, biotin, or flourochromes.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

8. Claims 1-5, 8, 10-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over De Vries et al (PNAS 95:12340-12345, 1998) and Rousset et al (Oncogene 16:643-654, 1998) and as evidenced by the specification, and further in view of Campbell (Monoclonal antibody technology, Elsevier Science Publishers, pages 1-32, 1986) and Harlow et al (antibodies, A laboratory manual, Cold Spring Harbor Laboratory, page 322, 1988) as applied to claims 1, 2, 8, 10-15 above, and further in view of Adair et al (WO 91/09967, published 7/11/91) and Green et al (Nature genetics 7:13-21, 1994).

Claims 1, 2, 8, 10-15 have been described supra. Claims 3-5 recite wherein the antibody is chimeric, humanized and human.

The primary and secondary references above have been described supra. The primary and secondary references does not teach a chimeric, humanized or human antibody. These deficiencies are taught by Adair et al and Green et al.

Adair et al teach methods of humanizing antibodies comprising chimeric antibodies for human therapy and to prevent HAMA response.

Green et al teach human antibodies for lower immunogenicity in humans.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a humanized or chimeric or human antibody to the protein of De Vries et al and Rousset et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a humanized or chimeric or

human monoclonal antibody to the protein of De Vries et al and Rousset et al because Rousset et al teach the TIP-2 protein interacts with the HTLV-1 Tax oncoprotein and the oncoprotein has been established to be associated with induction of tumors in transgenic mice (see page 643) and TIP-2 is a human protein that interacts with HTLV-1. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a humanized or chimeric or human monoclonal antibody to the protein of De Vries et al and Rousset et al because Green et al teach methods of producing human antibodies that reduce the immunogenicity when compared to mouse antibodies in treating human diseases. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a humanized or chimeric or human monoclonal antibody to the protein of De Vries et al and Rousset et al because Adair et al teach methods of humanized and methods comprising chimeric antibodies for therapy in humans to reduce the immunogenicity in humans compared to mouse antibodies. Thus, since the TIP-2 protein is associated with an oncoprotein it would be obvious to produce a human, humanized, or chimeric antibody to the protein.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY HELMS
PATENT EXAMINER